REMARKS

Applicants request favorable consideration and entry of the above Amendment, which is supported by the disclosure in the present specification and the subject matter of the allowed claims. Furthermore, the Amendment is supported by the disclosure in the priority document enclosed herewith. Applicants submit that the above amendment is needed for proper disclosure and protection of the invention, and would not require substantial additional work on the part of the Office. Entry of the above Amendment is respectfully requested.

Respectfully submitted,

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FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES

SUN PHARMACEUTICAL INDUSTRIES LTD.

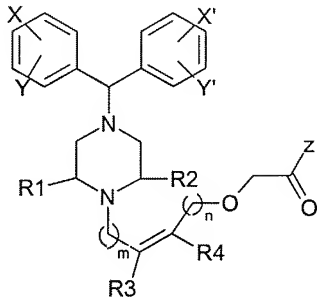
A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

The following specification describes the nature of this invention

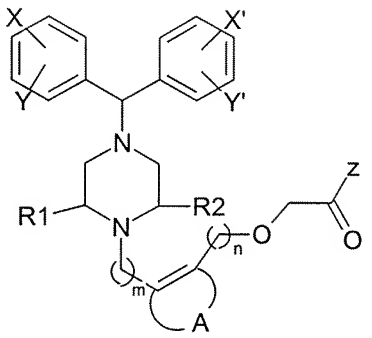
4-(DIARYLMETHYL)-1-PIPERAZINYL DERIVATIVES

The present invention relates to new antihistaminic compounds having 4-(diarylmethyl)-1-piperazinyl derivatives with alkenyl or alkynyl moiety substituted at the 1-position of the piperazine unit. The alkenyl or alkynyl moiety contains an alkyloxy carbonyl unit, wherein the carbonyl is part of a carboxylic acid function or its derivatives such as an ester, an amide, a hydroxamic acid or a hydrazide. These compounds include their non-toxic pharmaceutically acceptable acid addition salts and those derived from alkali metals, alkaline earth metals or amines including hydroxyalkylamines.

The present invention provides antihistaminic diarylmethylpiperazine derivatives and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III.& IV



I



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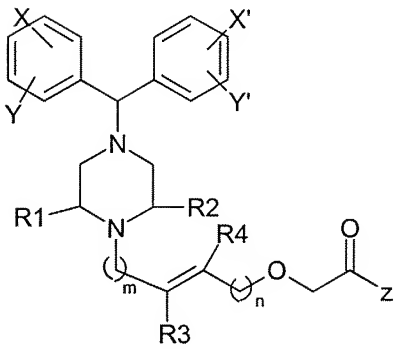
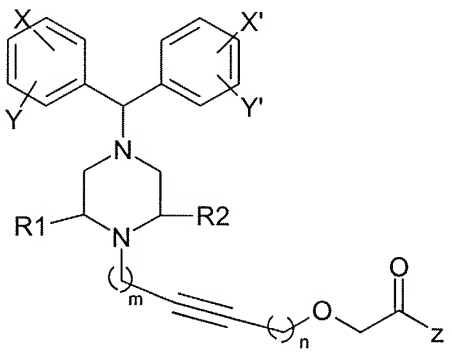


III



IV

wherein

X, Y, X' and Y'are selected from

- hydrogen atoms, substituted or unsubstituted alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbons 2 to 6.
- halogens viz. bromo, chloro, fluoro and iodo moities or haloalkyls such as trifluoromethyl
- amino, alkyl cycloalkyl or aryl substituted amino, hydroxy, alkoxy or aryloxy, mercaptoalkyl, or mercaptoaryl, alkyl or aryl sulfinyl or sulfonyl groups, substituted and unsubstituted sulfonamides or sulfonate esters.
- substituted or unsubstituted ureas or sulfonyl ureas
- carboxylic acids, acrylic acids, propargylic acids, or their derivatives such as amides, substituted amides with alkyl C1 –C5 substitution, or aryl substitution, or cyclic amides (C1 to C7), esters, N-hydroxyamides, or N-alkoxyamides.

R1, R2, R3 & R4 may be hydrogen, substituted or unsubstituted alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbon 2 to 6. The substituents R1 & R2 on the piperazinyl moiety may be either syn or anti to each other, syn being however preferred;

m and n are independently 1 to 6;

A in formula II represents -(CH2)n- wherein n=2 to 7 or -(CH2)x-D-(CH2)y- wherein D is O, NR, S or SO2, x and y are independently 1 to 6; or A is part of aryl or substituted aryl, heterocyclic aryl groups or substituted heterocyclic aryl groups containing one or more hetero atoms (viz., N, S, O);

Z is OH, OR, NRR', N(OR)R', N(R)-N(R)R', 

wherein R & R' represent hydrogen, alkyl groups (linear or branched), carbocyclic groups, polycyclic groups, aryl, heterocyclic aryl groups or substituted aryl and heterocyclic aryl or aralkyl groups, heterocycles and substituted heterocycles containing one or more of hetero atoms (viz., N, S, O), substituted or unsubstituted alkenyl or alkynyl groups of carbon 2 to 6;
and B represents -(CH2)n- wherein n=2 to 7 or -(CH2)x-D-(CH2)y where D is O, NR, S or SO2, x and y are independently 1 to 6.

The non-toxic, pharmaceutically acceptable salts may be acid addition salts of pharmaceutically acceptable acids such as organic acids like acetic, citric, succinic, maleic, fumaric, oxalic, benzenesulfonic, methanesulfonic, pamoic, xinafoic, ascorbic and the like or mineral acids such as hydrochloric, hydrobromic, sulfuric, phosphoric and the like. The pharmaceutically acceptable salts may also be salts derived from alkali metals (for example sodium, potassium and lithium), alkaline earth metals (for example calcium, magnesium) or amines including hydroxyalkylamines

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV including wherein X, Y, X' & Y' may be individually hydrogen or halogen or haloalkyl, most preferably hydrogen or halogen.

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein R1 & R2 may be hydrogen or alkyl groups, most preferably hydrogen.

A preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I & III wherein R3 & R4 may be hydrogen atom or alkyl groups, most preferably hydrogen.

Another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein m and n may be 1 to 2 and most preferably 1.

Another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formula II wherein A preferably represents -(CH2)n- wherein n=3 to 5, most preferably 3 to 4.

Yet another preferred embodiment of the present invention provides antihistaminic compounds containing diarylmethylpiperazines and their non-toxic pharmaceutically acceptable salts thereof of formulas I, II, III & IV wherein Z may be OH, OR, NRR', N(OR)R', wherein R & R' may be hydrogen, or alkyl groups, most preferably Z is OH.

Dated this 26th of March 2002

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED